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With the Author's compliments.

An Investigation into the Etiology of Phthisis.

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AN INVESTIGATION INTO THE ETIOLOGY OF PHTHISIS.

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This investigation is undertaken with the object of working out the morbid changes in the lungs which result in the formation of cavities, and endeavoring to prove the causal relation of the bacillus tuberculosis thereto. Also by inoculation experiments on animals to find out whether all forms of phthisis reproduce themselves in the same manner; the ape, as being the animal most nearly allied to man, being taken for this purpose. At the same time the clinical histories, physical signs, and symptoms of the cases from which material is taken are fully and carefully investigated to find out if different lesions in the lungs can be diagnosed thereby. A careful series of experiments are being carried off with inoculated animals to prove the value of various therapeutical measures, special apparatus and heated isolated rooms being arranged for that purpose.

I.

On the Histology of Tubercle.

BY HENEAGE GIBBES, M.D.

On reading the vast amount of work that has already been done on this subject it would seem that any further investigation was uncalled for; but the discovery of Koch's tubercle bacillus has produced a new

definition of tuberculosis, and now everything in the shape of lung or other disease that contains the tubercle bacillus is considered to be tuberculosis: while the old-fashioned term pulmonary phthisis is either left out altogether from the text-books, or else is mentioned as synonymous with tuberculosis.

It would, therefore, seem imperative that the processes set up by this bacillus and its relation to them should be thoroughly understood before this theory should be accepted. Such is, however, very far from being the case, as a perusal of some of the latest works on pathology will show.

It has always been a matter of wonder to me that this theory of Koch's should at once have met with almost universal acceptance with scarcely any corroborative evidence. As a proof that this is the case, in a paper by Dr. Harold C. Ernst, in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES for November, 1889, the following statement is made:

"The work showing the etiological relationship of the bacillus of tuberculosis to the disease was, to all intents and purposes, complete upon the publication of Koch's monograph upon the subject. Nothing more in the way of proof was actually needed, and, indeed, very little has been furnished."

Further on he states:

"What is accepted the scientific world over, that in the organism described by Koch we have the specific cause of this pathological change, and that without its activity we do not have tuberculosis in any form or under any conditions."

Dr. J. F. Payne, in his *Manual of General Pathology*, published in 1888, says in describing tuberculosis:

"Tuberculosis is the name given to the disease caused by the introduction of tubercle bacilli into the body."

Further on he gives the heading:

"Tuberculosis of the Lungs, or Pulmonary Phthisis."

Koch's discovery came at a very opportune time; this bacillus was the solution of a difficulty, and numbers of men at once accepted the new theory. The practical work in demonstrating the tubercle bacillus in sputum was also easy of accomplishment and enabled many men to get their names in print who otherwise would have languished in well-deserved obscurity.

Having thus the cause of the disease established, it would seem that nothing difficult would be found in describing the effects produced. From the earliest observations made on tuberculosis and phthisis down to those of the present day more than one form of lesion has been observed in the lungs, and from these differences arose the variety of opinion as to the unity or duality of phthisis, which has been now settled by the discovery of the bacillus tuberculosis.

The views of the older writers are so well known it is needless to recapitulate them here. Taking, therefore, the statements of writers of the present time, that is, since the discovery of Koch's bacillus, we will see how the unity of phthisis is established by them, for if B. tuberculosis is the virus of tuberculosis the unity of phthisis is a foregone conclusion. On turning, however, to various authorities on tuberculosis, we find that they all are obliged to describe a number of definite lesions in the lungs. Ziegler has quite a bewildering array of pathological processes in connection with diseases of the lungs.

Austin Flint, in Pepper's *System of Medicine*, says:

"There are two distinct varieties of morbid products in cases of phthisis, namely, the miliary granulations and the infiltrated deposit formerly distinguished as crude tubercle."

Loomis's *Practical Medicine*, 1889, says:

"Recent investigations have established a pathological unity in the morbid processes of pulmonary phthisis.

While all forms of tubercular disease must be considered identical in their origin, and the primary lesion in each to be tubercle, the wide variations in the morbid changes which are found in the lungs of phthisical subjects, *as well as the marked differences in their clinical history*,[1] compel us to recognize two distinct varieties of pulmonary tuberculosis."

Bristowe, in the sixth edition of his *Practice of Medicine*, makes a statement to the same effect.

Fagge, in the second edition of his *Principles and Practice of Medicine*, edited by Dr. Pye-Smith, states that all cases of phthisis are essentially of the same character; and further, that pneumonic phthisis is equivalent to phthisis which has advanced quickly, fibroid phthisis to one of which the course has been slow. He further states that it is necessary, both from a clinical and pathological point of view, to distinguish acute miliary tuberculosis from phthisis.

Dr. Payne says:

"Tuberculosis of the lungs or pulmonary phthisis is by far the most common disease. Here we recognize two forms distinguished by the manner in which the poison is introduced and distributed through the organs."

These references, which might be multiplied indefinitely, will serve to show that although the tubercle bacillus of Koch is recognized by all these writers as being the virus of the disease, yet they are unable to reconcile it with their clinical experience.

Nearly all writers vary in the classification they adopt of the varieties of phthisis; some include acute miliary tuberculosis, others leave it out; the same with fibroid phthisis. Dr. Payne's view that the lesion varies with its method of introduction is worth further notice, and we will see on what observations he founds his views. He divides tuberculosis into

[1] The italics are mine.—H. G.

the catarrhal and infective forms of phthisis. The catarrhal form, he states, occurs when the disease has entered the lungs through the respiratory channels; the infective, when it has followed the channels of the circulation, sanguineous or lymphatic. The infective form, he further states, agrees in its distribution with acute miliary tuberculosis. He also states, "the forms may be combined, the latter being developed out of the former or even *vice versa*." In describing these forms he puts them under two headings.

"1. *Pulmonary Phthisis.*—In most of the cases it is clear that the poison enters the organ by the respiratory channels.

"The process appears to be that the bacilli settle down in some portion of lung where there is little movement and the expulsive action of the ciliated epithelium of the bronchi is less energetic. Such a spot is clearly the apex, or it may be in spots where previously existing inflammation favors the lodgement and growth of the bacillus. Within the alveoli and possibly in the smallest bronchioles they set up changes resulting in the formation of a miliary tubercle. It is now clearly established that the tubercle is formed at first inside the alveoli, though at one time it was thought to belong to the interstitial structure of the lung.

"Thus we have the commonest lesion of phthisis which makes up a great part of the morbid changes in most phthisical lungs, viz, caseous or scrofulous broncho-pneumonia, or catarrhal pneumonia.

"This process may occur alone or may be accompanied by miliary tubercles.

"Caseous pneumonia arises from inhalation of the virus into the alveoli, while miliary tuberculosis, etc., are due to infection by bloodvessels and lymph channels (Watson Cheyne). Caseous pneumonia, *with or without visible tubercles*, may spread over a large part of the lungs and soon undergoes necrosis; this causes softening or breaking down, the lung tissue is thus destroyed.

"2. *Infective Tuberculosis of the Lung.*—If the tubercular virus be distributed by the pulmonary arterial system it becomes arrested at various places in the capillaries and a number of small tubercular foci are formed which may be compared to minute embolisms. This constitutes the process known as acute miliary tuberculosis of the lung.

"It may occur quite independently of any broncho-pneumonia or inflammatory process such as above described, which is proved by the fact that cases occur where the whole lung tissue is crepitant and normal but for the miliary tubercles, and where during life the physical signs of lung disease are absent."

I have quoted fully from Dr. Payne, as his is the most lucid explanation of the processes he has described, and now I will analyze his description and see how it will agree with the histology of tubercle as I am about to define it.

In the first place, his description of pulmonary phthisis is exactly what was always considered to be correct, a capillary bronchitis extending into and involving portions of the lung substance. He thinks the bacilli settle down where there is little movement and where the action of the cilia is less energetic; this, he says, is clearly the apex, but he gives no data on which his opinion is founded. Now, what proof have we that there is less movement in the apex of the lungs than in other parts of the organ? The statement has frequently been made that the air is not so readily changed

in the upper part of the lungs. I can see no foundation for this statement. Let anyone carefully examine a man in perfect health with erect carriage and he will see that all parts of the lung expand equally both in ordinary and forced inspiration, and I think most modern practical, not theoretical, physiologists will bear me out in this. Again, in women who wear corsets the costal type of respiration shows that the upper portion of the lungs is doing even more than its share of work; and are these women any more free from phthisis than men?

When the disease is established the patient stoops, and then the action of the upper part of the lung is impaired, but why? Because the disease has caused the stoop and consequent relaxation of the muscles' action on the upper part of the lung. As to the statement that the action of the cilia is less energetic, this is pure theory without a shadow of proof. He also says there may be spots of previously existing inflammation for the bacilli to lodge in. This seems an extraordinary statement. How are these inflammatory spots brought about that are ready for the bacillus to drop into and develop, and what has caused them? Why should they not be the disease itself producing a change in the tissues making a favorable nidus for these bacilli to grow in? He then states that changes take place within the alveoli resulting in the formation of a miliary tubercle. He has before described a miliary tubercle as composed of a fine reticular stroma and giant cells. He states that the tubercle is formed inside the alveolus, and informs us that "this is already established;" by whom he does not say.

We have, then, an inflammatory condition beginning in the bronchi and extending into the lungs, where it results in the formation of miliary tubercles. He then goes on further to state that the tubercle proper becomes mingled with the products of ordinary inflammation, so as to produce the appearance of broncho-pneumonia, and then says the process may occur alone or may be accompanied by miliary tubercles. This statement is so involved that it is difficult to know what is meant.

There are assumptions made here of which we are given no proof, and yet on them rests the foundation for the bacillary origin of the disease. Dr. Payne places after some of the statements he has made the name of Mr. Watson Cheyne, and we may infer that he has taken Mr. Cheyne's work to corroborate the theories he advances. It is therefore necessary to look up Mr. Cheyne's work to see how it does this.

In the London *Practitioner*, for April, 1883, Mr. Cheyne published a paper in which he describes the investigations he had made, and I find his work often quoted as entirely corroborating Koch's theory in regard to the bacillary origin of phthisis. Among many other positive statements he makes is this:

"In man we have the disease termed acute miliary tuberculosis, which resembles in every respect—histological structure, tendencies, and presence of

bacilli—the acute tuberculosis produced in animals by the inoculation of tuberculous material."

Numerous observers have disproved this, and I shall have occasion to allude to it again.

Mr. Watson Cheyne in the same paper describes and figures "a body which was apparently a parasite." It was pointed out to him by competent histologists at one of the societies where he showed the specimens from which this drawing was made, that what he thought a parasite was really a striped muscle fibre which occurs normally in the pulmonary vein of rabbits. Such faulty observation does not inspire reliance in his deductions.

Anyone reading the various descriptions of the lesions in tuberculosis cannot fail to see that the endeavor to make them fit into the bacillary view has caused a twisting of facts, an assumption of many things as proved which are not based on reliable work, and the adoption of theories without proof even attempted, so that we have now a situation where numerous writers accept a virus for a disease, the lesions of which they cannot even all describe alike, to say nothing of the origin of these lesions: some saying that tubercle is of connective tissue origin, others of epithelial; some saying the bacilli are always found in the giant cells, others that they have never found them there; while, as a climax, Watson Cheyne describes the formation of giant cells from epithelial cells and then figures the formation of a capillary bloodvessel from a giant cell.

It seems to me that this diversity of opinion as to the lesions in tuberculosis would be removed if the structure of a tubercle were well defined and its connection with the disease established. Most of the writers quoted describe two forms of tubercle, and say they occur in the same lung indiscriminately; and Dr. Payne even goes so far as to say the one may develop out of the other, or *vice versa;* and here lies the crucial point: if this is the case, the unity of phthisis is an established fact; but if these two forms *do not occur* in the same lung, then there are different lesions resulting in the formation of cavities, and it follows that the bacillus tuberculosis does not at one time form one lesion and at another time a totally different one. In other words, it is highly improbable that the bacillus is the virus of *both* diseases. Numerous descriptions have been written of the histology of tubercle by E. Wagner, Friedländer, and others, while Buhl and Hering have described acute miliary tuberculosis as disseminated catarrhal pneumonia. I shall not, however, refer further to their work, but take that of Klein in his *Anatomy of the Lymphatic System*, vol. ii., as here he describes the appearances found in the lungs of seven children that died of acute miliary tuberculosis. I have made thousands of sections of these very lungs and can speak positively of the appearance presented in them. All the cases except one had been diag-

nosed as acute miliary tuberculosis; in the one case the diagnosis was uncertain whether enteric fever or tuberculosis.

Klein found that the histological appearances in two of the cases differed entirely from the other five. The two cases he describes as follows:

"The abnormal masses (tubercles) correspond to groups of alveoli and infundibula, being filled with and distended by a fibrinous material that contains granules and small cells. . . . The structure of the alveolar wall is hardly distinguishable and its capillary bloodvessels not permeable, as is shown by the fact that in well-injected (artificially) specimens the injection does not extend into these capillaries . . . all through both lungs the nodules show the same histological characters. There was no trace of giant cells anywhere."

His description of the remaining five cases is too long to quote, but it amounts to this, that these differ entirely from the two first described, and the tubercles consisted of a reticular stroma containing one or more giant cells, while in the centre of the larger tubercles was a necrosed area. I have now before me a very large number of mounted sections from these seven cases, and also from a large number of cases I have obtained from time to time. They all can be divided absolutely into two classes: reticular and caseous tubercles.

I cannot agree with the conclusion he draws that the reticular form is only a later stage of the caseous, for two reasons: 1, in the large number of sections I have examined some would show a transition stage from caseous to reticular—this is certainly not the case; 2, in support of this view he supposes that the fibrinous material he describes in the centre of a caseous tubercle may be replaced by groups of cells or by a giant cell. I have in many sections the very first commencement of the formation of a reticular tubercle, and the process is this:

1. A number of round cells are found massed together in a small area of the lung tissue. 2. These cells assume a spindle shape, and at the same time the first formation of a giant-cell appears. At the same time new capillary bloodvessels are formed, and then the reticular tissue from the spindle-cells, or these processes may go on together. The tubercle now presents the appearance of a fibroid tissue with one or more giant cells in it, having patent bloodvessels containing Berlin blue injection material. I have always injected these lungs when practicable. As the tubercle grows, the fibroid tissue increases and assumes a more or less circular form and grows from within, so that giant cells are now in the periphery; after a time the centre necroses, I suppose from the contraction of the fibroid tissue cutting off the blood supply—at any rate, the injection will only now penetrate the reticular tissue. Several of these tubercles develop side by side until a number are fused together, and still some can be found in the mass in all stages of development. These

two forms of tubercle are indistinguishable to the naked eye, and are distributed through all parts of the lungs, but never together in the same lung.

From the above description it will be seen that the two forms of tubercle described agree entirely with those of Payne, only they do not occur in the same lung, nor are they capable of transformation the one into the other, or *vice versa*.

There now remains the relation of the tubercle bacillus to these two forms. On December 4, 1882, I read a paper at the Medical Society of London, in which I described the two forms of tubercle, and pointed out that in the caseous form every tubercle contained large numbers of bacilli; while in many cases of the reticular form they were absent altogether, and when present only existed in very small numbers and then isolated amongst the reticular tissue. I have since then carefully examined every case of acute miliary tuberculosis I have been able to obtain—and they are not a few—and I have found the same state of things in all of them. When the caseous form exists there will be the bacilli in the smallest tubercles, but I have never been able to find any in a commencing tubercle of the reticular form in its earliest stage. I have also never seen a bacillus in a giant-cell in the human lung. Hamilton, in the *Hand-book of Pathology*, vol. i., states that the giant-cells sometimes contain the tubercle bacillus, although rarely in man. Further on, he states there are many tubercles in which not a vestige of the bacillus can be seen. Dr. Payne says:

"In specimens from the human subject the giant cells very rarely contain bacilli. The writer has never seen them in that situation, and observers of much larger experience have confirmed this negative result. . . . . The bacilli are, on the other hand, very numerous in the caseous masses of human phthisis."

In speaking of tubercle Dr. Payne says:

"The structure known as acute miliary tubercle is now regarded as the essential type of the disease."

I have now given a description of the histology of tubercle based on the examination of thousands of sections taken from a large number of cases of this disease. From the information gained I feel justified in considering that the disease, acute miliary tuberculosis, is of two kinds, as shown by the difference in the structure of the tubercles and in the relation of the tubercle bacillus to them; the one being an acute inflammatory process localized throughout the lungs, the other a formation akin to granulation tissue, also localized, and from the mode of its growth prone to produce necrosis in the centre of the tubercles. What the relation of the tubercle bacillus is to these two forms remains to be proved.

Acute Phthisis.

Many pathologists complain that the physician uses a different classification to theirs, and that he distinguishes varieties of phthisis at the bedside which the pathologist does not recognize. And no wonder, when the pathologist is striving to make these varieties all fit into one theory as to their causation. A large number of clinicians of great experience will not admit that all forms of lung cavities come from one and the same cause; they know the physical signs, symptoms, or course of the disease will not allow this. In acute phthisis, either the phthisis florida of the German writers or that of a more chronic form, it can be shown that there are no tubercular formations such as have been described under miliary tuberculosis—I mean in those cases where there has been catarrhal pneumonia causing consolidation, which consolidation has not cleared up but has gone on to caseation and subsequent breaking-down, thus forming a cavity.

Tuberculosis.

On the other hand, in many cases where there are large cavities in the lungs, these are clearly seen to be caused by the breaking-down of tubercular masses, as in portions of the lung remaining the reticular tissue and giant-cells are plainly seen. From this I conclude that there are two distinct processes which form consolidations in the lungs and then break down, forming cavities; but these processes do not occur indiscriminately in the same lung. To prove this, Dr. G. C. Huber, of this University, made an investigation in my laboratory of the lungs taken from cases of phthisis. He embodied the results in a paper read before the State Medical Society at Kalamazoo in May last, and the paper was published in the *Medical News* of July 8, 1889.

He found 21 cases in all; 5 of these were fibroid phthisis, and were, therefore, discarded; of the remaining 16, sections were cut from various parts and the results were always the same—they were either cases of tuberculosis or of caseous phthisis, and the two forms were never mixed. I have examined an enormous number of lungs from phthisical cases during the last seven years, and my experience has always been the same.

The relation of the tubercle bacillus to these forms, also, is different; in the caseous form there are always large numbers of them, while in tuberculosis, where there is caseation and breaking down, they also occur, but not in anything like the number they do in the caseous form. I have also examined several cases of tuberculosis with large cavities without finding a single bacillus in several hundred sections. This is only what Koch himself admits, he having also found cases where there were no bacilli. The above are facts which can easily be verified by an ex-

amination of my specimens, and surely in the face of them no conscientious man can say that the tubercle bacillus is absolutely proved to be the virus of phthisis.

Fibroid Phthisis.

By this I mean a condition where the product of some acute inflammation, such as croupous pneumonia, has not cleared up, but has remained behind in patches; these have undergone various changes, but generally retain their characteristic appearance so far as to enable one to understand the primary change.

In my experience croupous pneumonia is the commonest form which produces a fibroid change. The unabsorbed residue sets up an irritation which is followed by increase of the normal fibrous tissue until large bands of this are seen in parts of the lungs; the process is a very chronic one, and is generally associated with much pigmentation and anthracosis. In these cases, at any rate in some of them, the consolidated material after a time caseates and breaks down, and in this can be found the tubercle bacilli. I have noticed one peculiarity in connection with this disease; that is, the formation of large giant-cells at the edges of the consolidation together with fibroid tissue resembling tubercles. This was of quite recent date and probably corresponded to the breaking down of the consolidation. In miners' and other phthisis caused by long-continued irritation the process is essentially the same—it results in the formation of dense fibrous tissue; the breaking down in these cases seems to be independent of the original disease. Of what is called true interstitial pneumonia I have no experience, never having seen a case; in fact, I rather doubt its existence.

I have already stated Mr. Cheyne's views as to the identity of the tubercles produced by inoculation in animals with those occurring spontaneously in the human subject. That these views are incorrect is absolutely certain; there is no formation of a reticular nature such as we find in a true miliary tubercle. In animals the inoculation produces nodular inflammatory masses with, in some cases, multinucleated cells; these masses often caseate, but do not generally break down and form cavities as in the human subject. I have found that there is a difference in the resulting nodule according to whether the material used for inoculation is taken from a case of caseous phthisis or from one of tuberculosis, and this difference is carried on to other animals inoculated from the first. I have not, however, been able yet to get sufficient data on this subject, from the great difficulty there is in this country in obtaining post-mortem examinations. Another point worthy of notice is the absence of the tubercle bacillus from the commencing nodules produced by inoculation. In all my numerous experiments on animals I have

never been able to find the bacillus in the very beginning of the nodular formation; it does not occur until the nodule becomes caseous. This differs entirely from the process in leprosy, where in the liver the change can be seen where only two or three cells are affected, and there invariably are several bacilli. A great deal of work has yet to be done before this interesting question is finally settled.